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Chronic hepatitis C virus infection and lymphoproliferative disorders: Mixed cryoglobulinemia syndrome, monoclonal gammopathy of undetermined significance, and B-cell non-Hodgkin lymphoma

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Abstract

Background and Aim

Chronic hepatitis C (CHC) has been associated with lymphoproliferative disorders (LPD) such as mixed cryoglobulinemia syndrome (MCS), monoclonal gammopathy of undetermined significance (MGUS), and B-cell non-Hodgkin lymphoma (B-NHL). The aim of the present study is to assess MCS, MGUS, and B-NHL prevalence in a cohort of CHC-infected patients and to evaluate the association of demographic, clinical, and virologic factors with the presence of LPDs.

Methods

A total of 121 CHC patients with LPDs (50 M, 71 F; mean age 61.5 ± 11.8) and 130 CHC patients without extrahepatic manifestations (60 M, 70 F; mean age 60.4 ± 9.2) were retrospectively enrolled from a cohort of 1313 CHC patients between January 2006 and December 2013. Patients with LPDs included: 25 patients with MCS (9 M, 16 F; mean age 60.2 ± 1.4), 55 patients with MGUS (18 M, 37 F; mean age 61.3 ± 12.1), and 41 patients with B-NHL (23 M, 18F; mean age 62.5 ± 11.0)

Results

Patients with MCS (25/1313; 1.9%), MGUS (55/1313; 4.2%), and B-LNH (41/1313; 3.1%) did not differ in age, severity of liver disease, HCV genotype, and response to antiviral therapy. Using multivariate logistic regression analysis, a positive association was found between the presence of cirrhosis and MGUS (odds ratio [OR] = 2.8924, 95% confidence interval [CI] 1.2693–6.5909; *P* = 0.012) and between cirrhosis and B-NHL (OR = 3.9407, 95%CI 1.7226–9.0153; *P* = 0.001), whereas no association with MCS diagnosis emerged.

Conclusion

Despite the pathogenetic mechanism of HCV-associated LPDs is still unclear, cirrhosis is an additional risk factor for the development of lymphoproliferative disorders in patients with chronic HCV infection.

Introduction

Hepatitis C virus (HCV) is both a hepatotropic and lymphotropic virus and is estimated to affect over than 180 million people worldwide.[1] Chronic hepatitis C (CHC)-infected patients have an increased risk of developing cirrhosis and hepatocellular carcinoma.[2] Furthermore, CHC has been associated with several extrahepatic manifestations including lymphoproliferative disorders (LPD) such as mixed cryoglobulinemia (MC), monoclonal gammopathy of undetermined significance (MGUS), and B-cell non-Hodgkin lymphoma (B-NHL).[3]

MC syndrome (MCS) is a symptomatic systemic vasculitis characterized by the deposition of immunocomplexes formed by HCV, anti-HCV polyclonal immunoglobulin (Ig) G and monoclonal or polyclonal IgM in type II or type III MC, respectively.[4] Low levels of cryoglobulins are usually found in up to 50% of HCV-infected patients and symptoms are generally absent or very mild, whereas only a minority of infected patients experiences a clinically evident MCS. The most common symptoms include purpura, arthralgia, fatigue, and diffuse vasculitis.[5]

MGUS is a benign B-cell LPD caused by a clonal expansion of plasma cells that produce a unique immunoglobulin and it is characterized by a low M-spike and no bone lesions or plasmacytosis in the marrow.[6]

Several study supported the association of HCV infection and B-NHL especially in countries with a high prevalence of HCV infection as Italy, Egypt, Japan, or southern US regions.[7] The role of HCV in lymphomagenesis is not fully clear, but may be related to a continuous stimulation of lymphocyte receptors by viral antigens leading to B-cell proliferation.[8]

The aim of the present study is to assess MCS, MGUS, and B-NHL prevalence in a cohort of CHC-infected patients and to evaluate the association of demographic, clinical, and virologic factors with the presence of LPDs.

Methods

Patients

This study included 121 cases (50 M, 71 F; mean age 61.5 ± 11.8) and 130 controls (60 M, 70 F; mean age 60.4 ± 9.2) tested positive for anti-HCV and/or HCV-RNA retrospectively enrolled from a total of 1313 CHC patients referred to the Division of Gastroenterology and Hepatology of San Giovanni Battista University Hospital of Turin between January 2006 and December 2013.

Cases included CHC patients with extrahepatic manifestations: 25 patients with MCS (9 M, 16 F; mean age 60.2 ± 1.4), 55 patients with MGUS (18 M, 37 F; mean age 61.3 ± 12.1), and 41 patients with B-NHL (23 M, 18 F; mean age 62.5 ± 11.0) (Table 1). Of the patients, 19 (76%) with MCS had type II cryoglobulinemia, whereas 6 (24%) showed type III. Among the 41 patients with B-NHL lymphoma, 15 (36.6%) had marginal zone lymphoma (MZL), 10 (24.4%) had diffuse large B-cell lymphoma (DLBCL), 4 (9.8%) had follicular lymphoma (FL), 1 (2.4%) lymphoplasmacytic lymphoma (LPL), 1 (2.4%) multiple myeloma, 1 (2.4%) chronic lymphocytic leukemia, and 9 (22%) other B-NHL not otherwise specified. Type II cryoglobulins were associated with B-NHL in 8 out of 41 (17%) patients (6 with MZL, 1 with LPL, and 1 with FL). All patients with aggressive B-NHL were followed by hematologists and treated with immune chemotherapy. Conversely, patients with indolent B-NHL were managed with antiviral treatment.

Table 1. Demographic, clinical, and virologic characteristics of patients with extrahepatic manifestations of CHC

		MCS	MGUS	B-LNH	*P*
Number		25	55	41	
Age, mean ± SD		60.2 ± 12.4	61.3 ± 12.1	62.5 ± 11.0	0.728
Gender, M/F		9/16	18/37	23/18	0.061
Diagnosis	CAH/Cirrhosis	19/6	40/15	25/16	0.166
HCV genotype	1	83%	58%	59%	0.099
	2	17%	33%	37%	0.276
	3	0%	4%	0%	0.321
	4	0%	4%	4%	0.601
Therapy	IFN	19%	11%	10%	
	IFN + RBV	57%	59%	58%	
	IFN + RBV + TPV/BOC	5%	3%	0%	
Outcome	Responders to HCV therapy	19%	37%	37%	0.272

B-NHL, B-cell non-Hodgkin lymphoma; BOC, boceprevir; CAH, chronic active hepatitis; F, female; IFN, interferon; M, male; MCS, mixed cryoglobulinemia syndrome; MGUS, monoclonal gammopathy of undetermined significance; RBV, ribavirin; SD, standard deviation; TPV, telaprevir.

Controls were selected on the basis of the absence of extrahepatic manifestation of HCV infection and were matched to the cases by age, gender, and HCV genotype. The main demographic, clinical, and virologic characteristics of the whole study patients are shown in Table 2. Cirrhosis was diagnosed by liver biopsy or by laboratory data and imaging findings (ultrasonography and transient elastography).

Table 2. Case and controls characteristics

		Cases	Controls	*P*
Number		121	130	
Age, mean ± SD		61.5 ± 11.8	60.4 ± 9.2	0.405
Gender, M/F		50/71	60/70	0.448
Diagnosis	CAH/Cirrhosis	84/37	113/17	0.001
HCV genotype	1	64%	65%	0.889
	2	31%	24%	0.289
	3	2%	7%	0.123
	4	3%	4%	0.999
HCV-RNA, median (range)	Log_{10} (IU/mL)	6.1 (4.9–7.0)	6.0 (2.9–7.6)	0.104
HCV therapy	IFN	13%	7%	
	IFN + RBV	60%	76%	
	IFN + RBV + TPV/BOC	2%	0%	
Outcome	Responders to HCV therapy	32%	41%	0.244

BOC, boceprevir; CAH, chronic active hepatitis; F, female; HCV, hepatitis C virus; IFN, interferon; M, male; RBV, ribavirin; SD, standard deviation; TPV, telaprevir.

The study complied with good clinical practice protocols and with the ethical rules stated in the Declaration of Helsinki (as revised in Tokyo 2004). The study has been approved by the institutional Ethics Committee and all patients gave their written informed consent prior to recruitment.

LPDs diagnosis

Cryoglobulins were isolated from patients' venous blood, allowed to clot at 37°C, and the serum was separated by centrifugation. The supernatant was incubated at 4°C for 7 days and examined for cryoprecipitate. MCS was diagnosed on the basis of serological findings (mixed cryoglobulins with rheumatoid factor activity) and clinical features such as purpura, arthralgia, fatigue, and vasculitis.[5, 9]

MGUS was defined as the presence of monoclonal protein of < 30 g/L and bone marrow clonal cells of < 10% with no evidence of multiple myeloma, other B-cell proliferative disorders or amyloidosis, according to the consensus definitions of the known monoclonal gammopathies by the International Myeloma Working Group.[10]

Diagnosis of B-NHL was achieved evaluating clinical, biochemical, radiological, and histological parameters. Clinical examination included vasculitis manifestations, B symptoms (fever, weight loss, night sweats), and lymphoid organ enlargement. Laboratory evaluation included full blood count and lymphocyte phenotype analysis in the peripheral blood. Radiologic evaluation included at least a chest X-ray and abdominal ultrasonography at the diagnosis and during follow-up. Bone marrow biopsy and/or lymph node biopsy was

performed in the case of abnormal lymphocyte phenotype analysis in the peripheral blood and lymphoid organ enlargement. B-NHL was categorized according to the World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues.[11]

Statistical analysis

Data were analyzed using Kruskal–Wallis and chi-squared test. Relative risk was estimated by odds ratio (OR) and 95% confidence interval (CI). A multivariate logistic regression analysis was performed to evaluate the association of demographic, virologic, and clinical factors with the presence of LPDs. A *P* value < 0.05 was considered statistically significant.

Results

The study included 121 CHC patients with LPD from a total of 1313 CHC patients evaluated between 2006 and 2013. Extrahepatic manifestations included patients with MCS (25/1313; 1.9%), MGUS (55/1313; 4.2%), and B-LNH (41/1313; 3.1%) who did not differ in age, severity of liver disease, HCV genotype, and response to antiviral therapy. Regarding gender, a trend of higher male patients among B-LNH group (56% male) compared with patients with MCS (33% male) and MGUS (36% male) was found (*P* = 0.061) (Table 1). Considering the whole population enrolled, a statistical significant difference in liver disease severity was found between cases and control. In fact, 31% of patients with LPD had a diagnosis of cirrhosis compared with 13% of controls (*P* = 0.001), whereas cirrhosis prevalence in the whole cohort of 1313 CHC patients was 14%. Conversely, no differences were found regarding other clinical and virologic parameters (Table 2).

Clinical and virologic factors associated with LPD were analyzed by univariate and multivariate logistic regression analysis. The results are shown in Table 3. Using univariate logistic regression analysis, there was a significant positive association between the presence of cirrhosis and LPD (OR = 2.9279, 95%CI 1.5439–5.5524; *P* = 0.001), which was reconfirmed by multivariate logistic regression analysis (OR = 3.0256, 95%CI 1.5605–5.8664; *P* = 0.001). Performing a multivariate logistic regression analysis to evaluate the association of demographic, clinical, and virologic factors with the diagnosis of MCS, MGUS, and B-LNH, a significant positive association between cirrhosis and MGUS (OR = 2.8924, 95%CI 1.2693–6.5909; *P* = 0.012), and between cirrhosis and B-NHL (OR = 3.9407, 95%CI 1.7226–9.0153; *P* = 0.001) was found (Tables 4, 5), whereas no significant association with MCS diagnosis emerged (Table 6).

Table 3. Univariate and multivariate logistic regression analysis of factors associated with the presence of lymphoproliferative disorders

	Cases	Controls	Univariate analysis		Multivariate analysis	
			OR 95% CI	*P*	OR 95%CI	*P*
Age, mean	61.5	60.4	1.0102 (0.9864–1.0348)	0.405	1.001 (0.9755–1.0253)	0.993
Female sex	59%	54%	1.2171 (0.7383–2.0064)	0.448	1.2889 (0.7672–2.1655)	0.338
Cirrhosis	31%	13%	2.9279 (1.5439–5.5524)	0.001	3.0256 (1.5605–5.8664)	0.001
SVR	32%	41%	0.6772 (0.3518–1.3037)	0.244	—	—
Genotype 1	64%	65%	0.9611 (0.5512–1.6728)	0.889	—	—

CI, confidence interval; OR, odds ratio; SVR, sustained virologic response.

Table 4. Univariate and multivariate logistic regression analysis of factors associated with the presence of MGUS

	MGUS	Controls	Univariate analysis		Multivariate analysis	
			OR 95% CI	*P*	OR 95%CI	*P*
Age, mean	61.3	60.4	1.0097 (0.9779–1.0426)	0.555	1.0014 (0.9691–1.0348)	0.933
Female sex	67%	54%	1.7619 (0.9103–3.4104)	0.093	1.9470 (0.9719–3.9205)	0.060
Cirrhosis	27%	13%	2.4926 (1.1399–5.4506)	0.022	2.8924 (1.2693–6.5909)	0.012
SVR	37%	41%	0.8366 (0.3508–1.9953)	0.688	—	—
Genotype 1	58%	65%	0.7049 (0.3508–1.4164)	0.326	—	—

CI, confidence interval; MGUS, monoclonal gammopathy of undetermined significance; OR, odds ratio; SVR, sustained virologic response.

Table 5. Univariate and multivariate logistic regression analysis of factors associated with the presence of B-NHL

	B-NHL	Controls	Univariate analysis		Multivariate analysis	
			OR 95% CI	*P*	OR 95%CI	*P*
Age, mean	62.5	60.4	1.0238 (0.9859–1.0631)	0.221	1.0150 (0.9753–1.0563)	0.464
Female sex	44%	54%	0.6708 (0.3309–1.3599)	0.268	0.6403 (0.3039–1.3491)	0.241
Cirrhosis	39%	13%	4.2541 (1.8952–9.5489)	< 0.001	3.9407 (1.7226–9.0153)	0.001
SVR	37%	41%	0.8296 (0.3030–2.2713)	0.715	—	—
Genotype 1	59%	65%	0.7792 (0.3335–1.8209)	0.565	—	—

B-NHL, B-cell non-Hodgkin lymphoma; CI, confidence interval; OR, odds ratio; SVR, sustained virologic response.

Table 6. Univariate logistic regression analysis of factors associated with the presence of MCS

	MCS	Controls	Univariate analysis		Multivariate analysis	
			OR 95% CI	*P*	OR 95%CI	*P*
Age, mean	60.2	60.4	0.9974 (0.9546–1.0422)	0.908	—	—
Female sex	64%	54%	1.5238 (0.6280–3.6976)	0.346	—	—
Cirrhosis	24%	13%	2.0991 (0.7346–5.9982)	0.166	—	—
SVR	19%	41%	0.3282 (0.0884–1.2189)	0.096	—	—
Genotype 1	83%	65%	2.5446 (0.8159–7.9359)	0.108	—	—

CI, confidence interval; MCS, mixed cryoglobulinemia syndrome; OR, odds ratio; SVR, sustained virologic response.

The majority of patients were treated for chronic HCV infection with dual therapy based on pegylated-interferon (PEG-IFN) and ribavirin (RBV) (60% of cases *vs* 76% of controls). Sustained virologic response (SVR) was achieved in 32% of cases and in 41% of controls (*P* = ns). In a multivariate logistic regression model adjusted for age and gender, the only factors associated with response to antiviral therapy were HCV genotype non-1 (OR = 5.2740, 95%CI 2.5611–10.8609; *P* < 0.001) and pre-therapy HCV-RNA levels (OR = 0.5867, 95%CI 0.3577–0.9623; *P* = 0.035) (Table 7).

Table 7. Univariate and multivariate logistic regression analysis of factors associated with response to antiviral treatment

	R	NR/Rel	Univariate analysis		Multivariate analysis	
			OR 95% CI	*P*	OR 95%CI	*P*
Age, mean	59.8	59.0	1.0082 (0.9759–1.0416)	0.623	1.0028 (0.9656–1.0414)	0.885
Male sex	50%	43%	1.2648 (0.6806–2.3505)	0.457	1.1210 (0.5579–2.2525)	0.748
CAH	84%	80%	1.7603 (0.7603–4.2471)	0.208	—	—
MCS	5%	12%	0.3462 (0.0947–1.2649)	0.109	—	—
MGUS	14%	16%	0.9519 (0.4067–1.2649)	0.910	—	—
B-LNH	11%	11%	0.9454 (0.3520–2.5391)	0.911	—	—
Genotype non-1	56%	20%	5.2071 (2.5980–10.4366)	< 0.001	5.2740 (2.5611–10.8609)	< 0.001
HCV-RNA, Log_{10} (IU/mL)	5.8	6.1	0.5781 (0.4139–0.8075)	0.001	0.586 (0.3577–0.9623)	0.035

B-NHL, B-cell non-Hodgkin lymphoma; CAH, chronic active hepatitis; CI, confidence interval; HCV, hepatitis C virus; MCS, mixed cryoglobulinemia syndrome; MGUS, monoclonal gammopathy of undetermined significance; NR, nonresponder; OR, odds ratio; R, responder; Rel, relapser.

Regarding hematologic response to antiviral therapy in patients with indolent B-NHL (MZL, FL, and LPL), 17 out of 20 patients were treated with PEG-IFN and RBV, whereas three patients presenting markers of advanced cirrhosis were not treated because of their risk of liver failure as side effect of IFN-based therapy. Among patients treated with PEG-IFN, nine patients experienced an SVR, whereas eight patients did not respond to treatment. Complete response of onco-hematological disease was obtained in six of the nine patients with SVR (66.7%), whereas two patients obtain a complete B-NHL remission after surgery and one patient obtain only a partial hematological response (> 50% lesions size decrease).[12]

Discussion

Several extrahepatic manifestations have been reported in the natural history of CHC. Furthermore, HCV is strongly associated with LPDs such as type II and III MC, and to monoclonal gammopathies ranging from “benign” MGUS to “malignant” B-NHL.[5, 13]

Cryoglobulins can be found in patients with HCV infection in more than 50% according to different studies.[3] In our study, we evaluated chronic HCV-infected patients with MCS, and we found a prevalence of 1.9% in agreement to previous published data that reported a prevalence of ≤ 5% of overt cryoglobulinemic vasculitis related to chronic HCV infection.[7]

The prevalence of monoclonal gammopathies without cryoglobulinemia among patients with chronic HCV infection is controversial, ranging from 2% to 11%,[6, 14, 15] whereas in the normal healthy population, MGUS is found in approximately 3% of persons of > 70 years of age and in about 1% of those > 50-year-olds.[16] In our study, 4.2% of CHC patients had a diagnosis of MGUS and the mean age was 61 years old. In fact, the frequency of MGUS in normal population appears to be lower and age-dependent, suggesting an association of HCV infection with an increased risk for MGUS occurrence at an earlier age. Moreover, these data support the hypothesis that prolonged antigenic stimulation may be involved in the development of monoclonal gammopathy.

Several studies reported an association of HCV infection with B-NHL, with DLBCL and MZL being the subtypes most consistently associated with HCV, providing additional support for the hypothesis that HCV could cause proliferation of specific B-cell clones because of chronic antigenic stimulation.[17-20] Moreover, a large-scale multicenter case–control study carried out in seven countries from 1998 to 2004

reported an association of HCV infection with DLBCL, MZL, and LPL, but no association with other lymphomas subtypes, which do not originate from germinal center or postgerminal center B cells.[21] In our study, the sample size of patients with B-NHL was not sufficient to explore deeply all lymphomas subgroups, but some evidence of higher prevalence of MZL and DLBCL compared with other lymphomas subtypes was found.

Other indirect evidences for a possible role of HCV infection in the genesis of lymphoma are found in reports in which therapy against HCV is associated with regression of lymphoma. A recent systematic review of 16 therapeutic studies pointed out a complete LPD remission in the 75% of CHC patients treated with IFN (with or without RBV), in contrast to HCV-negative subjects with B-NHL that did not respond to interferon, indicating that lymphoma remission in the HCV-infected patients is not due to a possible antiproliferative effect of IFN.[22] In our study, the majority of enrolled patients was treated for CHC with PEG-IFN and RBV (60% of cases *vs* 76% of controls), dual therapy being the standard of care for CHC treatment in the time period of patients inclusion. No association was found between clinical factors, such as severity of liver disease and presence of extrahepatic manifestations, with response to antiviral therapy, except for HCV genotype 1 and higher pretherapy HCV-RNA levels that resulted strongly associated with antiviral treatment failure. In agreement with data from literature,[22] our study reports complete remission of indolent B-NHL in six of the nine patients with SVR (66.7%), supporting both the use of antiviral therapy as first-line approach in HCV-associated indolent lymphomas and the plausible causal role of HCV in lymphomagenesis.

Currently, guidelines suggest to treat CHC patients with indolent lymphoma subtypes with antiviral therapy because of cumulative evidences showing promising rates of hematological remission after HCV eradication.[1, 23] Conversely, in the management of HCV-associated aggressive B-NHL, antiviral therapy may be recommended after immune chemotherapy with the aim to prevent B-NHL recurrence and others chronic hepatitis complications.[7]

The most common risk factors associated with extrahepatic manifestations of HCV infection are older age, female gender, and extensive liver fibrosis.[24] In our study, we found an approximately twofold elevated risk for LPDs among patients with a diagnosis of cirrhosis. Moreover, considering LPDs as single entities, cirrhosis resulted more strongly associated with MGUS (OR = 2.8924, 95%CI 1.2693–6.5909; $P = 0.012$) and, particularly, with B-NHL (OR = 3.9407, 95%CI 1.7226–9.0153; $P = 0.001$). Probably, extensive liver fibrosis and cirrhosis may have a role in helping antigenic stimulation by reducing the blood flow through the liver parenchyma, and consequently allowing the passage of numerous antigenic stimuli directly to systemic circulation, bypassing the liver filter activity of hepatic macrophages.[25]

The present study could be limited by the retrospective design that may have led to a selection bias of patients enrolled. Despite the controls that were matched to cases according to age, gender, and HCV genotype, the significant association between cirrhosis and MGUS and B-NHL could be the result of a possible controls selection bias. However, considering that the prevalence of cirrhosis in the whole population of 1313 CHC patients (14%) did not differ from the prevalence of cirrhosis in the control group (13%), the significant higher rate of cirrhosis that we found in patients with LPD (37%) is unlikely to be a consequence of patients selection bias.

Another possible limitation of this study is represented by the absence of systematic liver biopsy evaluation in all cirrhotic patients. Despite histological evaluation being considered the gold standard for liver fibrosis/cirrhosis assessment, in patients with impaired liver function, the presence of clinical signs, ultrasonographic features, and transient elastography measures compatible with cirrhosis was used for diagnosis.[26]

In conclusion, CHC infection can lead to several extrahepatic manifestations including LPDs, and cirrhosis appears to be an important risk factor for MGUS and B-NHL development. Despite the exact molecular

mechanism of HCV-associated lymphomagenesis being still unclear, the recent availability of IFN-free direct-acting antiviral drugs could considerably improve SVR, safety, and reduce the risk of HCV-related disease complications.

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